Raynaud's phenomenon (primary)

Search date May 2010

Janet Pope

ABSTRACT

INTRODUCTION: Raynaud's phenomenon is an episodic vasospasm of the peripheral arteries, causing pallor, followed by cyanosis and redness with pain, and sometimes paraesthesia. On rare occasions it can lead to ulceration of the fingers and toes (and in some cases of the ears or nose). This review focuses on primary (idiopathic) Raynaud's phenomenon, occurring in the absence of an underlying disease. The prevalence of primary Raynaud's phenomenon varies by sex, country, and exposure to workplace vibration. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for primary Raynaud's phenomenon? We searched: Medline, Embase, The Cochrane Library, and other important databases up to May 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 16 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: amlodipine, diltiazem, exercise, inositol nicotinate, keeping warm, moxisylyte (thymoxamine), naftidrofuryl oxalate, nicardipine, nifedipine, prazosin, and smoking cessation.

QUESTIONS

INTERVENTIONS

TREATMENTS

Likely to be beneficial

Trade off between benefits and harms

Unknown effectiveness

Covered elsewhere in Clinical Evidence

Raynaud's phenomenon (secondary)

To be covered in future updates

Biofeedback

Other drug treatments

Ceramic gloves

Footnote

*Categorisation based on consensus.

Key points

- Raynaud's phenomenon is episodic vasospasm of the peripheral arteries, causing pallor, followed by cyanosis and redness with pain and sometimes paraesthesia. On rare occasions it can lead to ulceration of the fingers and toes (and in some cases of the ears or nose). This review focuses on primary (idiopathic) Raynaud's phenomenon occurring in the absence of an underlying disease.

  Prevalence, which varies by sex and country, is around 3% to 5% in most population studies, 80% to 90% of which is primary Raynaud's phenomenon, and is slightly higher in women than in men.

  Attacks may last from several minutes to a few hours, and long-term sufferers of initially idiopathic Raynaud's phenomenon can later go on to display features of underlying disorders such as scleroderma.

- Nifedipine seems to reduce the frequency and severity of Raynaud's attacks, although it is associated with high rates of adverse effects such as tachycardia, headache, and flushing.
- Moxisylyte may be helpful in reducing frequency of attacks in primary Raynaud's phenomenon.

  We found no evidence of sufficient quality to judge the effectiveness of amlodipine or diltiazem in treating primary Raynaud's phenomenon.

- Other drug treatments, such as nicardipine, naftidrofuryl oxalate, inositol nicotinate, and prazosin, may successfully treat primary Raynaud's phenomenon, but we found no studies large enough to enable us to draw firm conclusions.
- We found no evidence examining the efficacy of lifestyle changes, such as keeping warm, smoking cessation, and exercise, in treating and preventing Raynaud's phenomenon.

DEFINITION

Raynaud's phenomenon is episodic vasospasm of the peripheral arteries, causing pallor, followed by cyanosis and/or erythema, which can cause pain and sometimes paraesthesia, and, rarely, ulceration of the fingers and toes (and, in some cases, of the ears or nose). Primary or idiopathic Raynaud's phenomenon (Raynaud's disease) occurs without an underlying disease. Secondary Raynaud's phenomenon (Raynaud's syndrome) occurs in association with an underlying disease — usually connective tissue disorders, such as scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, or polymyositis. This review excludes secondary Raynaud's phenomenon. **Diagnosis:** The diagnosis of Raynaud's phenomenon is by a history of clearly demarcated pallor of digit(s), followed by at least one other colour change (cyanosis, erythema), which is usually precipitated by cold. A good history, physical examination, and laboratory results can help rule out secondary Raynaud's phenomenon. Review of symptoms or signs for connective tissue disease should be done. Laboratory testing may include full blood count (FBC), ESR, and ANA with pattern if connective tissue diseases are suspected. Magnification of the nailbeds to observe abnormal capillaries is also important in order to rule out Raynaud's phenomenon associated with connective tissue diseases.

INCIDENCE/ PREVALENCE

The prevalence of primary Raynaud's phenomenon varies by sex, country, and workplace exposure to vibration. One large US cohort study (4182 people) found symptoms in 9.6% of women and 8.1% of men, of whom 81% had primary Raynaud's phenomenon. [1] Smaller cohort studies in Spain have estimated the prevalence of Raynaud's phenomenon to be 3.7% to 4.0%, of which 90% is primary Raynaud's phenomenon. [2] [3] One study in Japan (332 men, 731 women) found symptoms of primary Raynaud's phenomenon in 3.4% of women and 3.0% of men. [4] A study of 12,907 people in the UK reported that 4.6% of people had demarcated finger blanching with cold exposure. [5]

AETIOLOGY/ RISK FACTORS

The cause of primary Raynaud's phenomenon is unknown. [6] There is evidence for genetic predisposition, [7] [8] usually in those with early-onset Raynaud's phenomenon (aged under 40 years). [9] One prospective observational study (424 people with Raynaud's phenomenon) found that 73% of sufferers first developed symptoms before 40 years of age. [9] Women are at higher risk than men (OR 3.0, 95% CI 1.2 to 7.8, in 1 US case control study of 235 people). [10] The other known risk factor is occupational exposure to vibration from tools (symptoms developed in about 8% with exposure *v* 2.7% with no exposure in 2 cohorts from Japan). [11] [12] People who are obese may be at lower risk. [10] Exposure to cold or heightened emotion can worsen symptoms.

PROGNOSIS

Attacks may last from several minutes to a few hours. One systematic review (search date 1996, 10 prospective observational studies, 639 people with primary Raynaud's phenomenon) found that 13% of long-term sufferers later manifested an underlying disorder, such as scleroderma. [13] Complications, such as digital ulcers, are extremely rare in primary Raynaud's phenomenon. Rarely, primary Raynaud's phenomenon can progress to secondary. This progression occurs most commonly in people with auto-antibodies (e.g., antinuclear antibodies), increased ESR, and/or abnormal nailbed capillaries, and occurs at a rate of 2% for suspected secondary Raynaud's phenomenon and 1% for secondary Raynaud's phenomenon, annually. [14]

AIMS OF INTERVENTION

To reduce the number and severity of attacks; to prevent tissue damage; to minimise adverse effects of treatment.

OUTCOMES

Raynaud's attacks: including frequency, severity, impact, and duration of symptoms (as assessed by patient diary); severity assessed by visual analogue scales, Likert scales, or the Raynaud's Condition Score; [15] **digital ulceration**, including rates, size, and healing. **Adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal May 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to May 2010, Embase 1980 to May 2010, and The Cochrane Database of Systematic Reviews May 2010 (online; 1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language. RCTs had to contain 20 or more individuals, of whom 80% or more were followed up. For drug interventions, RCTs had to be at least single-blinded (we excluded all studies described as "open", "open label", or not-blinded). For non-drug interventions, open and not-blinded studies were acceptable. There was no minimum length of follow-up required to include studies. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying

the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. We searched for any RCTs comparing included options in the review versus placebo or versus each other in people with primary Raynaud's, and included all RCTs of sufficient quality. Many RCTs included people with both primary and secondary Raynaud's phenomenon. We excluded RCTs in which <50% of people had primary Raynaud's phenomenon, or where the type of Raynaud's was unclear. We also excluded RCTs in which attacks were experimentally induced (e.g., by dipping the hands in cold water) or which did not assess clinical outcomes. Some RCTs compared changes in symptoms from baseline within each treatment group rather than directly comparing outcomes between treatment groups. These have been described in the comment sections. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics, such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 17). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for primary Raynaud's phenomenon?

OPTION NIFEDIPINE

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .
- Nifedipine seems to reduce the frequency and severity of Raynaud's attacks, although it is associated with high rates of adverse effects, such as tachycardia, headache, and flushing.

Benefits and harms

Nifedipine versus placebo:

We found one systematic review (search date 2003; 13 RCTs [11 RCTs of crossover design]). [16] Most RCTs identified by the review also included people with a diagnosis other than primary Raynaud's phenomenon. In such cases, the review included the RCT if a subset of people with primary Raynaud's phenomenon could be identified separately and their outcome assessed independently, or if >75% of people had primary Raynaud's. The review noted various methodological limitations of the identified RCTs; see further information on studies for full details. The review also noted calcium-channel blockers as a class; see further information on studies for results.

Raynaud's attacks

Compared with placebo Nifedipine may reduce the frequency and severity of Raynaud's attacks in people with primary Raynaud's phenomenon (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of Raynaud's attacks					
[16] Systematic review	Number of people in analysis not reported 10 RCTs in this analysis	**Frequency of ischaemic attacks** with nifedipine with placebo Absolute results not reported	WMD –6.05, 95% CI –11.19 to –0.19 P = 0.04 Potential for bias in meta-analysis; see further information on studies for full details	○○○	nifedipine
Severity of Raynaud's attacks					
[16] Systematic review	Number of people in analysis not reported 5 RCTs in this analysis	**Severity of ischaemic attacks (measured on a 10-cm visual analogue scale)** with nifedipine	WMD –1.81 95% CI –3.08 to –0.54 P = 0.005	○○○	nifedipine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with placebo Absolute results not reported	Potential for bias in meta-analysis; see further information on studies for full details		
[16] Systematic review	Number of people in analysis not reported 5 RCTs in this analysis	**Improvement in ischaemic attacks (measured on a 5-point scale; no further definition of the scale reported)** with nifedipine with placebo Absolute results not reported	WMD –1.11 95% CI –1.38 to –0.85 P = 0.005 Potential for bias in meta-analysis; see further information on studies for full details	○○○	nifedipine

Digital ulceration

No data from the following reference on this outcome. [16]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] RCT **Crossover design** **3-armed trial**	22 people In review [16]	**Adverse effects (not further detailed)** 10/22 (45%) with nifedipine 10 mg 16/22 (72%) with nifedipine 20 mg 6/22 (27%) with placebo	Significance not assessed		
[18] RCT **Crossover design**	26 people In review [16]	**Adverse effect** 16/21 (76%) with nifedipine Not reported with placebo			
[19] RCT	Number of people not reported In review [16]	**Oedema** 24% with nifedipine 0% with placebo	P = 0.01	○○○	placebo
[19] RCT	Number of people not reported In review [16]	**Flushing** 8% with nifedipine 0% with placebo	P = 0.01	○○○	placebo
[19] RCT	Total number of people not reported In review [16]	**Tachycardia** 2 people with nifedipine 0 people with placebo	Significance not assessed		
[20] RCT	39 people In review [16]	**Overall adverse effects** with nifedipine with placebo Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[20] RCT	39 people In review [16]	**Palpitations** 7/18 (39%) with nifedipine 1/18 (6%) with placebo	P <0.05	○○○	nifedipine
[21] RCT **Crossover design**	23 people In review [16]	**Adverse effects (post-crossover results)** 14/23 (61%) with nifedipine 2/23 (9%) with placebo Adverse effects included headaches, flushing, and ankle swelling	P = 0.05	○○○	placebo
[22] RCT **Crossover design**	34 people In review [16]	**Adverse effects (post-crossover results) , 12 weeks** 26/34 (76%) with nifedipine 5/34 (15%) with placebo Adverse effects included flushing, headache, and oedema	Significance not assessed		

Further information on studies

[16] **Methodological limitations of the identified RCTs** Most RCTs were small; the number of people included in each RCT with primary Raynaud's phenomenon ranged from three to 130 people (8 RCTs included 21 people or fewer with primary Raynaud's). The review noted that most RCTs included people with or without primary Raynaud's phenomenon, so the meta-analysis could be regarded as a subset analysis of the original RCTs, which could be biased if randomisation was not stratified in people with primary Raynaud's. It also noted that most RCTs that were crossover in design did not report pre-crossover results. Results after crossover may not allow for confounding factors, such as inadequate washout and the naturally variable course of Raynaud's phenomenon. The review included RCTs with a withdrawal rate of up to 35%. It noted that many of the included RCTs were of short duration (median 2 weeks, range 1−10 weeks) and used relatively low doses of nifedipine. **Effects of calcium-channel blockers as a class** The review also compared calcium-channel blockers as a group versus placebo. The meta-analysis included 12 RCTs of nifedipine, two RCTs of nisoldipine, two RCTs of nicardipine, and one RCT of diltiazem. It found that calcium-channel blockers as a group significantly reduced the frequency and the severity of attacks compared with placebo (frequency of ischaemic attacks: 17 RCTs; WMD –2.08, 95% CI –3.90 to –1.70; severity [measured on a 10-cm visual analogue scale]: 8 RCTs; WMD –1.39, 95% CI –2.20 to –0.58). However, most of the RCTs included in this analysis involved nifedipine.

Comment: **Clinical guide:**
The evidence suggests that nifedipine gives some benefit in reducing the frequency, severity, and number of primary Raynaud's attacks.

OPTION NICARDIPINE

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .
- Nicardipine may successfully treat primary Raynaud's phenomenon, but we found no studies large enough to enable us to draw conclusions.

Benefits and harms

Nicardipine versus placebo:

We found two RCTs. [23] [24]

Raynaud's attacks

Compared with placebo We don't know whether nicardipine is more effective at reducing the frequency, duration, or severity of ischaemic attacks at 6 to 8 weeks in people with primary Raynaud's phenomenon (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of Raynaud's attacks					
[23] RCT **Crossover design**	69 people with primary Raynaud's phenomenon	**Frequency of ischaemic attacks (post-crossover results) , 8 weeks** 4.9 attacks/week with nicardipine 5.8 attacks/week with placebo	Mean difference: 0.9 95% CI 0 to 2.2 P = 0.02 Data reported are post-crossover results and should be interpreted with caution; see further information on studies for full details	○○○	nicardipine
[24] RCT **Crossover design**	25 people (16 with primary Raynaud's phenomenon and 9 people with secondary Raynaud's phenomenon)	**Mean frequency of ischaemic attacks (post-crossover results) , 6 weeks** 4.4 attacks/day with nicardipine (30 mg twice daily) 4.4 attacks/day with placebo Analysis of 16 people with primary Raynaud's phenomenon	Reported as not significant P value not reported The RCT is likely to have been too small to detect a clinically important difference in outcomes Data reported are post-crossover results and should be interpreted with caution; see further information on studies for full details	⟷	Not significant
Severity of Raynaud's attacks					
[23] RCT **Crossover design**	69 people with primary Raynaud's phenomenon	**Overall disability (mean score post-crossover; measured on a 10-cm visual analogue scale, where 0 represented no disability) , 8 weeks** 2.6 with nicardipine 3.3 with placebo	P = 0.018 Data reported are post-crossover results and should be interpreted with caution; see further information on studies for full details	○○○	nicardipine
[23] RCT **Crossover design**	69 people with primary Raynaud's phenomenon	**Severity of ischaemic attacks (post-crossover results; measured on a scale of 1–4, where 1 represented mild and 4 highly severe) , 8 weeks** 1.36 with nicardipine 1.55 with placebo	Mean difference: 0.2 95% CI 0 to 0.4 P value reported as not significant Data reported are post-crossover results and should be interpreted with caution; see further information on studies for full details	⟷	Not significant
[24] RCT **Crossover design**	25 people (16 with primary Raynaud's phenomenon and 9 people with secondary Raynaud's phenomenon)	**Mean severity of ischaemic attack (post-crossover results; measured on a 10-point scale, where 0 represented no pain) , 6 weeks** 3.5 with nicardipine (30 mg twice daily) 3.7 with placebo Analysis of 16 people with primary Raynaud's phenomenon	Reported as not significant P value not reported The RCT is likely to have been too small to detect a clinically important difference in outcomes Data reported are post-crossover results and should be interpreted with caution; see further information on studies for full details	⟷	Not significant
[24] RCT **Crossover design**	25 people (16 with primary Raynaud's phenomenon and 9 people with secondary Raynaud's phenomenon)	**Mean duration of ischaemic attack (post-crossover results) , 6 weeks** 13 minutes with nicardipine (30 mg twice daily) 11 minutes with placebo Analysis of 16 people with primary Raynaud's phenomenon	Reported as not significant P value not reported The RCT is likely to have been too small to detect a clinically important difference in outcomes Data reported are post-crossover results and should be interpreted with caution; see further information on studies for full details	⟷	Not significant

Digital ulceration

No data from the following reference on this outcome. [23] [24]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] RCT **Crossover design**	69 people with primary Raynaud's phenomenon	**Withdrawals due to adverse effects** 5/69 (7%) with nicardipine 2/69 (3%) with placebo	Significance not assessed		
[24] RCT **Crossover design**	25 people (16 with primary Raynaud's phenomenon and 9 people with secondary Raynaud's phenomenon)	**Withdrawals because of adverse effects** 2/16 (13%) with nicardipine 1/16 (6%) with placebo Adverse effects included flushing, headache, and palpitations	Significance not assessed The RCT is likely to have been too small to detect a clinically important difference in outcomes		

Further information on studies

[23] [24] The results of the crossover trials should be viewed with caution, as no pre-crossover results were available, and results may not allow for confounding factors, such as inadequate washout and the naturally variable course of Raynaud's phenomenon.

Comment: **Clinical guide:**
Nicardipine has been less well studied in primary Raynaud's phenomenon than nifedipine, but it may decrease the frequency of Raynaud's attacks.

OPTION AMLODIPINE

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .
- We found no evidence of sufficient quality to judge the effectiveness of amlodipine in treating primary Raynaud's phenomenon.

Benefits and harms

Amlodipine versus placebo:

We found no RCTs that reported between-group comparisons of amlodipine versus placebo (see comment).

Further information on studies

Comment: We found one RCT that presented within-group comparisons of changes in outcomes from baseline (24 people, 15 with primary Raynaud's phenomenon, crossover design, outcomes assessed after crossover). [25] It found that amlodipine significantly reduced the number of acute attacks a week from baseline at 7 weeks (from 11.8 attacks/week at baseline to 8.6 attacks/week after treatment; P <0.001) and reduced the severity of attacks from baseline (from a discomfort score of 7.8 at baseline to 5.1 after treatment). However, the RCT did not assess the significance of the difference in frequency and severity of attacks between groups. It found that amlodipine was associated with ankle oedema (55% of people taking amlodipine *v* 0% of people taking placebo), flushing, and headaches compared with placebo (10–20% with amlodipine *v* 0% with placebo). [25] The RCT included people with secondary Raynaud's phenomenon, so results may not be applicable in people with primary Raynaud's phenomenon.

Clinical guide:
We cannot necessarily generalise the benefits of dihydropyridine calcium-channel blockers such as nifedipine to amlodipine, as it has not been primarily studied in RCTs solely in the treatment of primary Raynaud's phenomenon.

OPTION DILTIAZEM

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .
- We found no evidence of sufficient quality to judge the effectiveness of diltiazem in treating primary Raynaud's phenomenon.

Benefits and harms

Diltiazem versus placebo:

We found no RCTs that met *Clinical Evidence* inclusion criteria (see comment).

Further information on studies

Comment: One crossover RCT (30 people, 19 with primary Raynaud's phenomenon, outcomes assessed after crossover) found that diltiazem significantly reduced the number and duration of attacks over 8 weeks compared with placebo (mean reduction in attacks from baseline: 22.9/month with diltiazem *v* 4.6/month with placebo; P = 0.01; mean reduction in duration from baseline: 444 minutes/month with diltiazem *v* 160 minutes/month with placebo; P <0.01). [26] The results of this RCT should be interpreted with caution as it reported comparisons from baseline, thus removing the benefits of randomisation, and analysis was not by intention to treat (8/30 [27%] people withdrew from the trial). Two people withdrew from the trial because of adverse effects (rash or headache) while taking diltiazem. The RCT included people with secondary Raynaud's phenomenon, so results may not be fully applicable in people with primary Raynaud's phenomenon.

OPTION NAFTIDROFURYL OXALATE

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .
- Naftidrofuryl oxalate may successfully treat primary Raynaud's phenomenon, but we found no studies large enough to enable us to draw conclusions.

Benefits and harms

Naftidrofuryl oxalate versus placebo:

We found one RCT. [27]

Raynaud's attacks

Compared with placebo Naftidrofuryl oxalate may reduce the duration and intensity of Raynaud's attacks, and impact on daily activities, at 2 months in people with primary Raynaud's phenomenon (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of Raynaud's attack					
[27] RCT	102 people, 87 with primary Raynaud's phenomenon	**Duration of ischaemic attacks , 2 months** with naftidrofuryl oxalate (600 mg/day) with placebo Absolute results not reported	P <0.05 Results may not be generalisable to people with primary Raynaud's; RCT included people with secondary Raynaud's	○○○	naftidrofuryl oxalate
[27] RCT	102 people, 87 with primary Raynaud's phenomenon	**Intensity of ischaemic attacks , 2 months** with naftidrofuryl oxalate (600 mg/day) with placebo Absolute results not reported	P <0.001 Results may not be generalisable to people with primary Raynaud's; RCT included people with secondary Raynaud's	○○○	naftidrofuryl oxalate
[27] RCT	102 people, 87 with primary Raynaud's phenomenon	**Impact of ischaemic attacks on daily activities , 2 months** with naftidrofuryl oxalate (600 mg/day) with placebo Absolute results not reported	P <0.05 Results may not be generalisable to people with primary Raynaud's; RCT included people with secondary Raynaud's Clinical benefit of result unclear; see further information on studies for full details	○○○	naftidrofuryl oxalate

Digital ulceration

No data from the following reference on this outcome. [27]

Adverse effects

No data from the following reference on this outcome. [27]

Further information on studies

[27] The RCT demonstrated a reduced impact of attacks on daily activities. This outcome measurement was not used in other trials, so we cannot compare the relative benefits of this treatment option compared with other drugs in the treatment of primary Raynaud's phenomenon.

Comment: **Clinical guide:**
Naftidrofuryl oxalate is not routinely used to treat Raynaud's phenomenon.

OPTION INOSITOL NICOTINATE

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .

- Inositol nicotinate may successfully treat primary Raynaud's phenomenon, but we found no studies large enough to enable us to draw conclusions.

Benefits and harms

Inositol nicotinate versus placebo:

We found two RCTs. [28] [29]

Raynaud's attacks

Compared with placebo Inositol nicotinate may reduce the frequency and duration of ischaemic attacks at 12 weeks in people with primary Raynaud's phenomenon (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of Raynaud's attacks					
[28] RCT	23 people with primary Raynaud's phenomenon	**Number and duration of ischaemic attacks , 84 days** with inositol nicotinate (4 g/day) during the winter with placebo Absolute results not reported The RCT reported that people taking inositol nicotinate had fewer and shorter attacks	Reported as not significant P value not reported The RCT is likely to have been too small to detect a clinically important difference between groups	⟷	Not significant
[29] RCT	65 people, 54 with primary Raynaud's phenomenon	**Improvement in attacks (score of 0–1) , 12 weeks** 19/34 (56%) with inositol (2 g twice daily) 11/31 (35%) with placebo Improvement in attacks measured on a 5-point scale: from 0 (no problem) to 5 (very severe)	RR 1.58 95% CI 0.90 to 2.76 Results may not be generalisable to people with primary Raynaud's; RCT included people with secondary Raynaud's	⟷	Not significant

Digital ulceration

No data from the following reference on this outcome. [28] [29]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] RCT	65 people, 54 with primary Raynaud's phenomenon	**Withdrawal due to adverse effects (gastrointestinal disturbance and dizziness)** 3/34 (9%) with inositol (2 g twice daily) 2/31 (6%) with placebo	Significance not assessed		

No data from the following reference on this outcome. [28]

Further information on studies

Comment: **Clinical guide:**
Inositol is not usually used for the treatment of primary or secondary Raynaud's phenomenon.

OPTION PRAZOSIN

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .
- Prazosin may successfully treat primary Raynaud's phenomenon, but we found no studies large enough to enable us to draw conclusions.

Benefits and harms

Prazosin versus placebo:

We found one RCT. [30]

Raynaud's attacks

Compared with placebo Prazosin may be more effective at reducing the number and duration of attacks at 6 weeks, but may be no more effective at reducing the severity of attacks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of Raynaud's attacks					
[30] RCT **Crossover design**	24 people, 14 with primary Raynaud's phenomenon	**Mean frequency of ischaemic attacks (post-crossover results) , 6 weeks** 2.5 attacks/day with prazosin (1 mg twice daily) 4.1 attacks/day with placebo	P = 0.003 Results should be interpreted with caution; see further information on studies for full details	○○○	prazosin
Severity of Raynaud's attacks					
[30] RCT **Crossover design**	24 people, 14 with primary Raynaud's phenomenon	**Duration of ischaemic attacks (post-crossover results) , 6 weeks** 21.9 minutes with prazosin (1 mg twice daily) 29.9 minutes with placebo	P = 0.02 Results should be interpreted with caution; see further information on studies for full details	○○○	prazosin
[30] RCT **Crossover design**	24 people, 14 with primary Raynaud's phenomenon	**Mean severity of ischaemic attacks (post-crossover results; measured on a 10-point scale, where 0 represented no pain) , 6 weeks** 4.1 with prazosin (1 mg twice daily) 4.8 with placebo	P = 0.11 Results should be interpreted with caution; see further information on studies for full details	⟷	Not significant

Digital ulceration

No data from the following reference on this outcome. [30]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] RCT **Crossover design**	24 people, 14 with primary Raynaud's phenomenon	**Adverse effects (including dizziness and palpitations)** 50% with prazosin (1 mg twice daily) 29% with placebo Absolute numbers not reported	Significance not assessed		

Further information on studies

[30] The results of the RCT should be viewed with caution as no pre-crossover results were available and results may not allow for confounding factors, such as inadequate washout and the naturally variable course of Raynaud's phenomenon. The RCT included people with secondary Raynaud's phenomenon, so results may not be fully applicable in people with primary Raynaud's phenomenon.

Comment: **Clinical guide:**
The common adverse effects of prazosin may outweigh any benefits in treating primary Raynaud's phenomenon in most people. Because of this, prazosin is rarely used in the treatment of Raynaud's phenomenon.

OPTION MOXISYLYTE (THYMOXAMINE)

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .
- Moxisylyte may reduce the frequency of attacks in primary Raynaud's phenomenon, but we found no studies large enough to enable us to draw firm conclusions.

Benefits and harms

Moxisylyte versus placebo:

We found one systematic review (search date 2007), [31] which reported one RCT comparing moxisylyte with placebo.

Raynaud's attacks

Compared with placebo Moxisylyte may be more effective than placebo at reducing the frequency of Raynaud's attacks at 2 weeks, but may be no more effective at reducing the severity or duration of attacks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of Raynaud's attacks					
[31] Systematic review	41 people with primary Raynaud's phenomenon Data from 1 RCT Crossover trial	**Proportion of people with fewer Raynaud's attacks , at 4 weeks after crossover** 19/33 (57%) with moxisylyte 10/33 (30%) with placebo Absolute results not reported	P <0.02 The review did not report pre-crossover results	○○○	moxisylyte

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of Raynaud's attacks					
[31] Systematic review	41 people with primary Raynaud's phenomenon Data from 1 RCT Crossover trial	**Proportion of people who reported that their Raynaud's attacks were more severe , at 4 weeks after crossover** 7/33 (21%) with moxisylyte (40 mg 4 times daily) 18/33 (54%) with placebo Absolute results not reported	The review did not report pre-crossover results; as data were unavailable for 37% to 39% of participants, so no statistical analyses carried out See further information on studies		
Duration of Raynaud's attacks					
[31] Systematic review	41 people with primary Raynaud's phenomenon Data from 1 RCT Crossover trial	**Proportion of people with reduced duration of Raynaud's attacks , at 4 weeks after crossover** 15/33 (45%) with moxisylyte (40 mg 4 times daily) 9/33 (27%) with placebo Absolute results not reported	The review did not report pre-crossover results; as data were unavailable for 37% to 39% of the participants, no statistical analyses were carried out See further information on studies		

Digital ulceration

No data from the following reference on this outcome. [31]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[31] Systematic review	41 people with primary Raynaud's phenomenon Data from 1 RCT	**Adverse effects , at 4 weeks after crossover** 13/33 (39%) with moxisylyte (40 mg 4 times daily) 3/33 (9%) with placebo Absolute results not reported	RR 4.33 95% CI 1.36 to 13.81 See further information on studies for full details of adverse effects	●●○	placebo

Further information on studies

[31] This review reports on a RCT comparing moxisylyte (40 mg 4 times daily) versus placebo. The authors of the review point out that, as data were unavailable for 37% to 39% of the participants, they did not carry out any statistical analyses for the outcomes of severity or duration of Raynaud's attacks. **Adverse effects** Adverse effects reported in the systematic review [31] included dyspepsia, heartburn, flushing, and changes in taste. These were each reported by two or more participants while taking moxisylyte, and by no participants while taking placebo. However, the actual number of people reporting each adverse effect was not reported. One person was withdrawn from the treatment group because of an embolus deemed by the trial authors not to be drug related. Three people were withdrawn while taking placebo because of adverse effects.

Comment: **Clinical guide:**
In general, moxisylyte (thymoxamine) is not currently used in the treatment of primary Raynaud's phenomenon.

OPTION KEEPING WARM

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .
- Most clinicians recommend avoiding the cold, if possible, to prevent Raynaud's attacks, but we found no trials assessing its effects.

Benefits and harms

Keeping warm:

We found no RCTs evaluating keeping warm in people with primary Raynaud's phenomenon.

Further information on studies

Comment: **Clinical guide:**
Although we found no RCTs of sufficient quality in this area, most clinicians recommend avoiding the cold, if possible, to prevent Raynaud's attacks.

OPTION EXERCISE

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .
- We found no RCT evidence examining the efficacy of exercise in treating and preventing Raynaud's phenomenon.

Benefits and harms

Exercise:

We found no RCTs evaluating exercise in people with primary Raynaud's phenomenon.

Further information on studies

Comment: **Clinical guide:**
It is uncertain what effect exercise would have on primary Raynaud's phenomenon.

OPTION SMOKING CESSATION

- For GRADE evaluation of interventions for Raynaud's phenomenon (primary), see table, p 17 .
- We found no evidence examining the efficacy of lifestyle changes, such as smoking cessation, in treating and preventing Raynaud's phenomenon.

Benefits and harms

Smoking cessation:

We found no RCTs evaluating smoking cessation in people with primary Raynaud's phenomenon.

Further information on studies

Comment: **Clinical guide:**
It is uncertain what effect smoking cessation would have on Raynaud's phenomenon.

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Moxisylyte One systematic review added, [31] which reports one RCT comparing moxisylyte versus placebo. It found that moxisylyte may reduce the frequency of attacks in primary Raynaud's phenomenon. Categorisation unchanged (Unknown effectiveness), as there remain insufficient data to draw conclusions.

REFERENCES

1. Brand FN, Larson MG, Kannel WB, et al. The occurrence of Raynaud's phenomenon in a general population: the Framingham Study. *Vasc Med* 1997;2:296–301.[PubMed]
2. Rodriguez Garcia JL, Sabin Ruiz J. Raynaud's phenomenon. *Rev Clin Esp* 1989;184:311–321. [In Spanish][PubMed]
3. Riera G, Vilardell M, Vaque J, et al. Prevalence of Raynaud's phenomenon in a healthy Spanish population. *J Rheumatol* 1993;20:66–69.[PubMed]
4. Inaba R, Maeda M, Fujita S, et al. Prevalence of Raynaud's phenomenon and specific clinical signs related to progressive systemic sclerosis in the general population of Japan. *Int J Dermatol* 1993;32:652–655.[PubMed]
5. Palmer KT, Griffin MJ, Syddall H, et al. Prevalence of Raynaud's phenomenon in Great Britain and its relation to hand transmitted vibration: a national postal survey. *Occup Environ Med* 2000;57:488–452.[PubMed]
6. Wigley FM. Raynaud's phenomenon. *Curr Opin Rheumatol* 1993;5:773–784.[PubMed]
7. Smyth AE, Hughes AE, Bruce IN, et al. A case-control study of candidate vasoactive mediator genes in primary Raynaud's phenomenon. *Rheumatology (Oxford)* 1999;38:1094–1098.[PubMed]
8. Freedman RR, Mayes MD. Familial aggregation of primary Raynaud's disease. *Arthritis Rheum* 1996;39:1189–1191.[PubMed]
9. Planchon B, Pistorius MA, Beurrier P, et al. Primary Raynaud's phenomenon. Age of onset and pathogenesis in a prospective study of 424 patients. *Angiology* 1994;45:677–686.[PubMed]
10. Keil JE, Maricq HR, Weinrich MC, et al. Demographic, social and clinical correlates of Raynaud phenomenon. *Int J Epidemiol* 1991;20:221–224.[PubMed]
11. Komura Y, Yoshida H, Nagata C, et al. Differences in the prevalences of Raynaud's phenomenon in general populations living in a mountain area and in a plain area. *Nippon Koshu Eisei Zasshi* 1992;39:421–427. [In Japanese][PubMed]
12. Mirbod SM, Inaba R, Iwata H. A study on the vibration-dose limit for Japanese workers exposed to hand-arm vibration. *Ind Health* 1992;30:1–22.[PubMed]
13. Spencer-Green G. Outcomes in primary Raynaud phenomenon: a meta-analysis of the frequency, rates, and predictors of transition to secondary diseases. *Arch Intern Med* 1998;158:595–600.[PubMed]
14. Hirschl M, Hirschl K, Lenz M, et al. Transition from primary Raynaud's phenomenon to secondary Raynaud's phenomenon identified by diagnosis of an associated disease: results of ten years of prospective surveillance. *Arthritis Rheum* 2006;54:1974–1981.[PubMed]
15. Merkel PA, Herlyn K, Martin RW, et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum* 2002;46:2410–2420.[PubMed]
16. Thompson AE, Pope JE. Calcium channel blockers for primary Raynaud's phenomenon: a meta-analysis. *Rheumatology (Oxford)* 2005;44:145−150.[PubMed]
17. Challenor VF, Waller DG, Hayward RA, et al. Vibrotactile sensation and response to nifedipine dose titration in primary Raynaud's phenomenon. *Angiology* 1989;40:122–128.[PubMed]
18. Gjorup T, Kelbaek H, Hartling OJ, et al. Controlled double-blind trial of the clinical effect of nifedipine in the treatment of idiopathic Raynaud's phenomenon. *Am Heart J* 1986;111:742–745.[PubMed]
19. Raynaud's Treatment Study Investigators. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon. Results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med* 2000;160:1101–1108.[PubMed]
20. Sarkozi J, Bookman AA, Mahon W, et al. Nifedipine in the treatment of idiopathic Raynaud's syndrome. *J Rheumatol* 1986;13:331–336.[PubMed]
21. Corbin DO, Wood DA, Macintyre CC, et al. A randomized double blind cross-over trial of nifedipine in the treatment of primary Raynaud's phenomenon. *Eur Heart J* 1986;7:165–170.[PubMed]
22. Waller DG, Challenor VF, Francis DA, et al. Clinical and rheological effects of nifedipine in Raynaud's phenomenon. *Br J Clin Pharmacol* 1986;22:449–454.[PubMed]
23. French Cooperative Multicenter Group for Raynaud Phenomenon. Controlled multicenter double-blind trial of nicardipine in the treatment of primary Raynaud phenomenon. *Am Heart J* 1991;122:352–355.[PubMed]
24. Wollershiem H, Thien T. Double-blind placebo-controlled crossover study of oral nicardipine in the treatment of Raynaud's phenomenon. *J Cardiovasc Pharmacol* 1991;18:813–818.[PubMed]
25. La Civita L, Pitaro N, Rossi M, et al. Amlodipine in the treatment of Raynaud's phenomenon. A double-blind placebo-controlled crossover study. *Clin Drug Invest* 1997;13:126–131.
26. Rhedda A, McCans J, Willan AR, et al. A double blind controlled crossover randomized trial of diltiazem in Raynaud's phenomenon. *J Rheumatol* 1985;12:724–727.[PubMed]
27. Davinroy M, Mosnier M. Double-blind clinical evaluation of naftidrofuryl in Raynaud's phenomenon. *Sem Hop Paris* 1993;69:1322–1326. [In French]
28. Sunderland GT, Belch JJF, Sturrock RD, et al. A double blind randomised placebo controlled trial of Hexopal in primary Raynaud's disease. *Clin Rheumatol* 1988;7:46–49.[PubMed]
29. Murphy R. The effect of inositol nicotinate (Hexopal) in patients with Raynaud phenomenon — a placebo-controlled study. *Clin Trials J* 1985;22:521–529.
30. Wollershiem H, Thien T, Fennis J, et al. Double-blind, placebo-controlled study of prazosin in Raynaud's phenomenon. *Clin Pharmacol Ther* 1986;40:219–225.[PubMed]
31. Vinjar B, Stewart M. Oral vasodilators for primary Raynaud's phenomenon. In: The Cochrane Library, Issue 4, 2010. Chichester: John Wiley & Sons, Ltd. Search date 2007.[PubMed]

Janet Elizabeth Pope
Rheumatologist
St Joseph's Health Care Rheumatology Centre
London, Ontario
Canada

Competing interests: JP declares that she has no competing interests.

Disclaimer

The information contained in this publication is intended for medical professionals. Categories presented in Clinical Evidence indicate a judgement about the strength of the evidence available to our contributors prior to publication and the relevant importance of benefit and harms. We rely on our contributors to confirm the accuracy of the information presented and to adhere to describe accepted practices. Readers should be aware that professionals in the field may have different opinions. Because of this and regular advances in medical research we strongly recommend that readers' independently verify specified treatments and drugs including manufacturers' guidance. Also, the categories do not indicate whether a particular treatment is generally appropriate or whether it is suitable for a particular individual. Ultimately it is the readers' responsibility to make their own professional judgements, so to appropriately advise and treat their patients. To the fullest extent permitted by law, BMJ Publishing Group Limited and its editors are not responsible for any losses, injury or damage caused to any person or property (including under contract, by negligence, products liability or otherwise) whether they be direct or indirect, special, incidental or consequential, resulting from the application of the information in this publication.

GRADE **Evaluation of interventions for Raynaud's phenomenon (primary).**

Important outcomes			Digital ulceration, Raynaud's attacks						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for primary Raynaud's phenomenon?									
13 (unclear) [16]	Raynaud's attacks	Nifedipine versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for incomplete reporting of results, poor crossover methodology, and poor follow-up. Directness point deducted for RCTs including people with other conditions
2 (94) [23] [24]	Raynaud's attacks	Nicardipine versus placebo	4	–3	0	–1	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and poor crossover methodology. Directness point deducted for broad inclusion criteria
1 (102) [27]	Raynaud's attacks	Naftidrofuryl oxalate versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for broad inclusion criteria
2 (88) [28] [29]	Raynaud's attacks	Inositol nicotinate versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for broad inclusion criteria
1 (24) [30]	Raynaud's attacks	Prazosin versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and poor crossover methodology. Directness point deducted for broad inclusion criteria
1 (41) [31]	Raynaud's attacks	Moxisylyte versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and results being unavailable for over a third of participants for 2 measures of outcome. Directness point deducted for high withdrawal rate

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.